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Anatomy

HISTOPATHOLOGICAL EFFECTS OF DOXORUBICIN ON HEART OF WISTAR ALBINO RATS.

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ABSTRACT

Introduction: - Ideal anticancer drugs should eradicate cancer cells without harming normal tissues. Unfortunately, no currently available agents meet these criteria, and clinical use of these drugs involves a weighing of their benefits against their toxicity in search for a favourable therapeutic index.

Methods: - experimental animals were divided into 4 groups, control, low dose, therapeutic and high dose respectively. After giving respective doses and sacrificing the animals organs were taken and observed grossly and on under light microscopy.

Result: - microscopic changes were observed in all groups except control group. Low dose group showed less change while therapeutic group showed most of the changes which were observed by other authors. High dose group showed marked toxic changes.

Conclusion: - The present study showed that the toxicity pattern is almost same in low and therapeutic doses of doxorubicin, and this could be of immense value while treating the carcinoma patients while in high doses it cause severe toxicity on heart.

KEYWORDS : Doxorubicin, Histopathological.

Introduction: Cancer is basically a disease of cells characterized by a shift in the control mechanisms that govern cell proliferation and differentiation. The problem of cancer is universal. In developed countries, cancer is ranked as the second commonest cause of death, while in developing countries, it is third next to infectious and cardiovascular diseases. Doxorubicin (DXR), also known as Adriamycin, an anthracycline compound, is one of such natural products. DXR was originally isolated from a colony of streptomyces in 1957 and was shown to have significant activity in patients with acute myeloid leukemia.[1]

Materials and methods: Albino rats (Wistar strain) of either sex, weighing 125-160 grams were used for current experimental studies. They were procured from animal house, Government Medical College, Jammu. The clearance for the use of animals for experimental purpose was obtained from Animal Institutional Ethical Committee constituted for the before purpose. Animals were housed in polypropylene cages (6/cage) with dust free rice husk as bedding material under laboratory conditions with controlled environment of temperature of 25±2^{o}C , humidity (16% ± 10%) and 12 hours light/dark cycle (16- 18) as per Committee for the purpose of Control and Supervision of Experiment on Animals (CPCSEA), Indian guidelines. They were provided standard rodent chaw/feed and water ad-libitum. Subjecting them for experimentation, animals were given a week's time to acclimatize with laboratory conditions. Animals were fasted for 24 hours before experimentation.

The principal of Rationalization, Refinement and Reduction (3 “R's”) was strictly followed while undertaking the following experiment.

Experimental Design: The animals were divided into 4 groups with each group consisting of 6 animals.

GROUP 1 was administered weekly intraperitoneal injections of 3ml of sterile distilled water and it served as a healthy control.

GROUP 2 was administered a weekly low dose of doxorubicin (0.2 mg/kg body weight) intraperitoneal injection.

GROUP 3 was given a weekly therapeutic dose of doxorubicin (1mg /kg body weight) intraperitoneal injection.

GROUP 4 received a single intraperitoneal toxic dose of doxorubicin (20mg/kg body weight).

The above dosing schedules were adapted after going through studies conducted by **El-Sayyed H et al.[2], Sule A et al.,[3] and Shivakumar P et al.[4]**

The animals were sacrificed after 48 hours of the administration of final dose of drugs as per the prescribed methods by CPCSEA.

After sacrificing the animals, hearts were isolated and fixed in 10% buffered formalin solution and processed to prepare 5 micron thick paraffin sections. Paraffin sections were stained by using H&E/other relevant staining. Histological sections were examined by light microscopy to assess the degree of toxicity. The histopathological findings among the 4 groups were compared to achieve relevant conclusions.

Result: In *control group* NO 1:- no gross and microscopic changes were observed.

In the *LOW DOSE GROUP* NO 2:- There were no gross changes present. Microscopically, infiltration of inflammatory cells was seen with mild vascular congestion in between muscle fibres.

In the *THERAPEUTIC DOSE GROUP* NO 3:- No gross change was seen. Histologically, multifocal haemorrhages were present with increased distance between muscle fibres indicating vascular congestion of muscle fibres (fig 1).

In DOSE *the HIGH GROUP* NO 3:- No gross changes were detected. Under light microscopy, muscle fibres showed necrosis with pyknotic nuclei. Multifocal hemorrhages were also seen in between muscle fibres (fig 2).

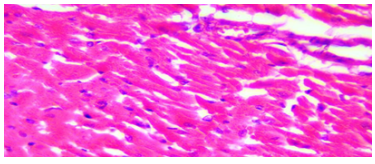

Fig 1. Heart showing interstitial edema(therapeutic dose 400X).

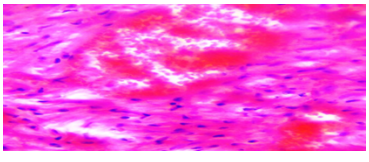

Fig 2. Heart showing marked vascular congestion with interstitial hemorrhage(high dose 400X).

Discussion : The purpose of the present study was to evaluate at our best the toxicity profile of the drug doxorubicin histologically in Wistar albino rats in order to suggest whether to modify the present therapeutic dosage of this drug for avoiding its toxicities on the heart.

In the control group which was given normal saline only, no gross or microscopical changes were seen under study. In the low dose group, no gross changes were seen. Microscopically, infiltration of inflammatory cells was seen with mild vascular congestion in between muscle fibres. At therapeutic dose of 1 mg/kg body weight there was cloudy swelling, loss of striations and multifocal hemorrhage in cardiac tissue. Moderate hypertrophy of myocardium was seen with extensive areas of hemorrhage. These findings were quite similar to the study done by Mettler FP et al., [5]. In the high dose group, there was myocytic degeneration, loss of striations and multifocal hemorrhage. This observation was in concurrence with most of the authors including **Rahman A et al.,[6] Mohamed AA et al.[7], Ihab AR and Ahmed AG[8] , Davey MS and Atlee CW[9] , Subashini R[10] , Khan MS et al.[11]**

Puri A et al., [12], Rasha AR and Abdella EM[13] on contrarary observed that the changes were not severe. They showed myocardial changes, not florid, in the form of hypertrophied muscle fibers with megaloblastic nuclei and scar areas of degenerated muscle fibres.

Summary: The present study was done for the purpose of studying the histopathological effects of doxorubicin on the heart of Wistar albino rats, so that appropriate dose adjustments and combination chemotherapy regimens can be suggested for cancer chemotherapy. It is therefore concluded from the present study that the toxicity pattern is almost same in low and therapeutic doses of doxorubicin, and this could be of immense value while treating the carcinoma patients while in high doses it cause severe toxicity on the heart.

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